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ABSTRACT

The task of the genetic counselor who identifies genetic causes of mental retardation and assists families to understand risk of recurrence is described. Considered are chromosomal genetic disorders such as Down's syndrome, inherited disorders such as Tay-Sachs disease, identification by testing the amniotic fluid cells (amniocentresis) in time for abortion, problems of identifying biochemical abnormalities, and kinds of decisions parents make with support from the genetic counselor. (MC)

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GENETIC COUNSELLING IN MENTAL RETARDATION

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Mental retardation may result from a wide variety of causes. It is the task of the genetic counsellor to identify those causes that are genetic in origin and to assist the family to understand the mechanism and the risk of recurrence. At this point, a classification of genetic types of mental retardation into (1) chromosomal, and (2) simply inherited, will be introduced.

Chromosomal

There are normally 46 chromosomes in the cells of the body. Two of these are concerned with sex determination. The female has a pair of similar sex chromosomes (XX) whereas the male has only one X and a smaller member responsible for his "maleness", the Y chromosome.

As a result of a faulty germ cell contributed by a parent, an individual may have an extra chromosome in his cells. If this is a non-sex chromosome, the individual is almost invariably mentally retarded. He (or she) will also have abnormal physical features, the pattern of which will be influenced by the particular chromosome involved.

One of the most frequent chromosomal abnormalities is Down's syndrome (mongolism), which is due to the presence of an extra chromosome No. 21. This is the smallest member of the human karyotype, except for the Y which is variable in size. As each chromosome is normally represented twice (one set having been received from each parent at the time of fertilization), the presence of an additional chromosome is referred to as trisomy for that member.

Trisomy for larger members of the human chromosome complement is less frequently observed since the degree of genetic imbalance is presumably greater and the effects are even more harmful than trisomy 21. The majority of these are lost as miscarriages or result in a severely disabled infant that dies within the first year of life.

Trisomy is the result of an accident of cell division called nondisjunction. Such accidents have an increasing tendency to occur in the germ cells of women as they become older. About one half of all children with Down's syndrome are born to mothers who are past the age of 35 years. The risk rises steeply during the terminal reproductive years and begins to exceed 1 in 100 at about the 40-year mark. This is about thirty times the average risk for a woman half that age. When a young couple has a child with Down's syndrome this is often an indication that their risk is greater than average for subsequent pregnancies.

In a small number of cases Down's syndrome is the result of a heritable chromosomal abnormality called a translocation. The translocation may be carried in a balanced form in the cells of one of the normal parents and in other normal relatives. It is important to identify these individuals as they have a high risk of bearing an affected child; for example, when a woman is a carrier of the translocation her risk of bearing a child with Down's syndrome may be as high as 1 in 10.

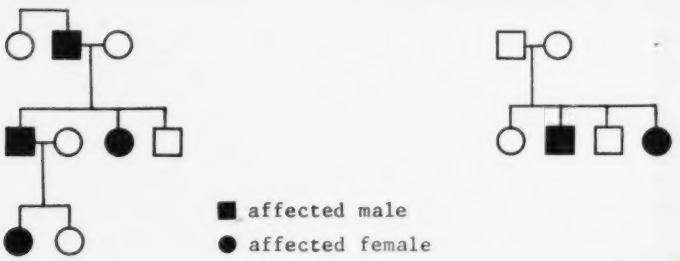
Most carriers are detected retrospectively; that is, after we have

examined the chromosomes of a child with Down's syndrome and discovered the characteristic translocation configuration. Carriers could be identified prospectively if we had the resources to screen the chromosomes of all newborns, and several pilot projects carried out to date indicate that this might be feasible.

Couples with increased risk for bearing a child with Down's syndrome can now avail themselves of a test (amniocentesis) that predicts Down's syndrome in time for abortion. We currently provide this test for women aged 35 or over, for couples of any age who have had a previous child with Down's syndrome, and for proven translocation carriers or other high risk parents.

Simply inherited disorders

These are due to single mutant genes of large effect that can not be observed by inspection of the chromosomes under the microscope. They are identifiable on the basis of their characteristic patterns of inheritance, as illustrated in the following pedigrees:



Transmission from one generation to the next, as in the pedigree on the left, is characteristic of an autosomal dominant. Recurrence of an identical abnormality in the same sibship, with no other occurrences in preceding generations or collateral relatives (pedigree on the right), is characteristic of a recessive.

The recurrence risks for simply inherited disorders are high. For example, there is a fifty percent chance that a person affected with tuberous sclerosis (autosomal dominant) will transmit it to his or her child. The hallmarks of this disease are epilepsy and papular lesions in a characteristic distribution on the face. As affected individuals are often retarded they are not likely to reproduce. The majority of cases occur sporadically as a result of rare new mutations and are not preventable by genetic counselling.

Parents who are carriers of a recessive trait are normal and are usually only identified after they have given birth to an affected child. The risk for sibs of being affected is 1 in 4. Affected persons, if they live to reproduce, are not likely to have an affected child unless by some rare coincidence they marry a carrier of the trait.

For a number of recessive disorders the clinically normal trait carriers can be identified by appropriate biochemical tests. Many Jewish communities are currently being screened for a gene that is known to be

prevalent among them that causes Tay-Sachs disease. This is a progressive disorder that begins in infancy and results in mental retardation, spasticity and death in early childhood. Couples at risk- i.e., both shown to be carriers, are advised of this risk before they conceive. If they desire to have children they can choose one of several options:

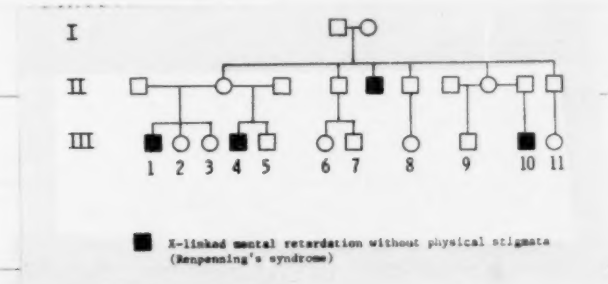
(1) They may disregard the risk and have children of their own (1 chance in 4 of a child being affected).

(2) They may adopt rather than bear children of their own.

(3) They may conceive with the knowledge that the fetus (amniotic fluid cells) can be tested for the presence of Tay-Sachs disease in time for abortion.

There is a growing list of recessively inherited biochemical abnormalities for which prenatal diagnosis by analysis of amniotic fluid cells is now possible.

The only mutant genes that can be assigned to one particular chromosome on the basis of the pedigree pattern are those that are located on the X chromosome. For example, mental retardation has occurred in the following pattern in a family that we have seen in our Genetics Clinic:



you will note that only males are affected and that transmission from one generation to the next is through normal females. This is characteristic of a recessive disorder due to a mutant gene situated on the X-chromosome. The normal males can not transmit the trait, nor can an affected male transmit it to his sons. Two of the five females in generation III have a fifty percent chance of being carriers and a consequent risk of bearing an affected male child. Can you identify them?

Our greatest limitation in counselling this particular family is that we have not succeeded in turning up any biochemical abnormality and we therefore have no means of positively identifying a female carrier until she bears an affected male child. For proven carriers, we can offer prenatal sex diagnosis and early termination of pregnancy if the fetus is male. As the risk that a male child will be retarded is fifty percent, this procedure will appeal to many couples who are faced with the actual prospect. It must be recognized that approximately one-half of the pregnancies terminated for this indication would have resulted in a normal male child, and this aspect raises conflicts in the minds of some people. For the two young girls referred to earlier (III:2&3) with an apriori risk of 50 % for the carrier state, the probability that a son will be affected is 1/2 x 1/2 = 1/4. As the chances that a male child will not be retarded are 3:1, selective abortion of male fetuses would be subject to even greater controversy. Hopefully, research on this disorder will soon provide a test for

the differentiation of affected from normal male fetuses *in utero* .

From the foregoing brief considerations it will be evident that the estimation of recurrence risks is merely one of many challenges that face the genetic counsellor. Of equal or greater importance is the ability to sort out heterogeneity (genetically distinct forms of the same clinical syndrome), to be aware of and utilize appropriate tests for the identification of clinically normal carriers of certain diseases, to devise screening programmes as advancing technology brings their costs within acceptable limits, to alleviate feelings of guilt, and to temper advice to meet the needs and philosophy of the individual.